REMARKS/ARGUMENTS

I. Claim Status

Independent claims 1, 38 and 51 have been amended to recite that the formulation is suitable for local administration to the lungs of the mammal such that a systemic effect is circumvented. Independent claim 27 has been amended to recite a step of locally administering to the lungs of a mammal a formulation comprising a hypertension reducing agent such that a systemic effect is circumvented. Dependent claims 2 has been amended to recite that the formulation is suitable for local administration to the lungs of a mammal by oral inhalation via nebulization. Dependent claim 28 has been amended to recite that the formulation is locally administered to the lungs of said mammal by oral inhalation via nebulization. Support for these amendments is found, at least, on paragraphs [0013], [0036] and [0066] of the published application (i.e. U.S. Publication No. 2004/0265238).

The status of the remaining claims are as follows:

Claims 3-4, 6-11, 17-20, 22-24, 31, 33, 35-37, 41-55 and 65 have been canceled.

Claims 1-2, 5, 12-16, 21, 25-30, 32, 34, 38-40, 51-55, 57-64, and 66-69 are pending.

II. Rejections Under 35 U.S.C. §112

Claims 1, 2, 5, 12-16, 21, 25-30, 32, 38-40 and 51-69 stand rejected under 35 U.S.C. §112, first paragraph, for failing to comply with the written description requirement. Specifically, the Office argues that the concentration range (i.e. 0.1 mg/ml to 15 mg/ml) in claims 1, 10, 27, 38 and 51 have no support. However, Applicant notes that the concentration range of "about 0.1 mg/ml to about 15 mg/ml" is found at claim 4 of the originally filed application. Thus, the currently claimed concentration is supported by the present application as originally filed. Applicant submits that the written description rejections have been overcome. Applicant requests withdrawal of this rejection.

III. Rejections Under 35 U.S.C. §102(b)

Claims 1-2, 12-14, 16 and 21 stand rejected under under 35 U.S.C. §102(b) as being anticipated by U.S. Patent No. 4,885,305 to Kiechel et al. (hereinafter "Kiechel"). To establish

an anticipation, a prior art reference must disclose the invention as set forth in the claim. Specifically, "a claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." M.P.E.P. §2131 citing *Verdegall Bros. v. Union Oil Co. of California,* 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). Applicant submits that Kiechel does not disclose every element of the currently claimed invention. Specifically, Kiechel does not disclose an inhalable formulation that is suitable for local administration to the lungs of a mammal such that a systemic effect is circumvented. Thus, Applicant respectfully traverses this rejection.

Kiechel is directed to a nasal pharmaceutical composition adapted to be "absorbed systemically through the nasal mucus" to treat hypertension. See abstract. The compositions include "calcium antagonists, also called calcium channel blocking agents." See column 1, lines 11-12. Preferred calcium antagonists include "1,4-dihydro-4-phenylpyridines such as Bay k 9320, felodipine, fluordipine, FR 7534, FR 34 235, FR 38 245, mesudipine, nicardipine, nifedipine, niludipine, nimodipine, nisoldipine, nitrendipine and SKF 24 260." See column 1, lines 60-64. "Suitable concentrations of active agent are for example about 0.1 to about 0.45% (i.e. 1 to 4.5 mg/ml)." See column 3, lines 44-46. Kiechel teaches that "up till now the calcium antagonists of the invention have not been administered systemically by nasal route for therapy for diseases." See column 1, lines 34-36. Kiechel teaches that "anatogonists ... are rapidly absorbed from the nasal mucus into the systemic blood circulation without significant first pass effect." See column 4, lines 38-40. As such, Keichel clearly teaches the benefits of administration of calcium antagonists systemically through the nasal mucus membranes.

However, Kiechel is silent regarding a formulation suitable for localized delivery to the lungs such that a systemic effect is circumvented as recited in independent claim 1, much less by oral inhalation via nebulization as recited in dependent claim 2. Instead Kiechel only teaches nasal formulations (i.e. nasal spray) suitable for absorption by the nasal mucus into the systemic blood circulation. See Column 2, line 60. At no point, does Kiechel mention a formulation suitable for administration to the lungs, much less to avoid a systemic effect. To the contrary, Kiechel teaches the systemic administration of calcium antagonists. Also, Kiechel does not provide any suggestion that a formulation, much less the formulations described in Kiechel,

could be suitable for localized administration to the lungs such that a systemic effect is avoided. Accordingly, Kiechel does not disclose each and every element of the currently claimed invention. Therefore, Kiechel does not anticipate independent claim 1, or any claims dependent thereon. Applicant requests withdrawal of the anticipatory rejection.

IV. Rejections under 35 U.S.C. §103(a)

To establish a prima facie case of obviousness there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the references or to combine reference teachings. Additionally, the prior are references must teach or suggest all claim limitations. Furthermore, the teaching or suggestion to make the claimed invention must both be found in the prior art, not in applicant's disclosure. Accordingly, Applicant submits that the Office has not established a *prima facie* case of obviousness.

A. Kiechel in view of Mead

Claims 15, 25-30, 32, 34, 38-40 and 51-69 stand rejected under 35 U.S.C. §103(a) as being obvious over Kiechel in view of U.S. Patent No. 4,885,305 to Mead et al. (hereinafter "Mead"). The Office acknowledges that Kiechel does not disclose adding a complexing agent. Thus, the Office relies on Mead for teaching a complexing agent.

Mead is directed to compositions including anticholinergics and endothelin antagonists that exhibit a synergistic effect in the treatment of respiratory tract diseases. Anticholinergics are a class of medications that inhibit parasympathetic nerve impulses by selectively blocking the binding of the neurotransmitter acetylcholine to its receptor in nerve cells. Endothelin antagonists block endothelin, a 21-amino acid vasoconstricting peptide produced primarily in the endothelium. Mead teaches that such compositions can be used for the treatment of pulmonary hypertension. See column 2, line 61. The compositions may be provided in the form of a propellant-free inhalable solution or suspension, wherein the solvent may be aqueous or alcoholic. See column 8, lines 64-67.

However, Mead does not cure the deficiencies of Kiechel discussed above. For instance, Mead does not teach or suggest a formulation including a calcium channel blocker suitable for

localized delivery to the lungs such that a systemic effect is circumvented nor the treatment of pulmonary hypertension by administering a formulation including a calcium channel blocker locally to the lungs of a mammal. Applicant notes that the current application was subject to a species election in which Applicant elected to prosecute a formulation comprising a calcium channel blocker. In fact, Mead is silent regarding calcium channel blockers. Additionally, Mead is silent regarding a formulation including a calcium channel blocker that is suitable for localized delivery to the pulmonary system. Instead, Mead is only concerned with the synergistic effect achieved from the combination anticholinergics and endothelin antagonists. Since Kiechel and Mead both fail to teach or suggest these elements, the combination thereof also fails to teach or suggest these elements as currently claimed. Accordingly, any combination of Kiechel and Mead does not teach of suggest all claimed elements as recited in independent claims 1, 27, 38 and 51 (or any claims dependent thereon). Therefore, the combination of Kiechel and Mead does not establish a *prima facie* case obviousness. Applicant requests withdrawal of this rejection.

Additionally, the necessary motivation for combining Kiechel and Mead in the manner suggested by the Office is lacking. Specifically, the skilled artisan would not be motivated to combine or modify the Kiechel calcium antagonist-based nasal compositions designed to be "absorbed systemically through the nasal mucus" with the Mead compositions which are in no way concerned with the administration of calcium antagonists, let alone administration of calcium antagonists systemically through the nasal mucus membranes. Moreover, Kiechel expresses no need for a complexing agent and Mead does not suggest that a complexing agent, such as EDTA, would be suitable for nasal application. In fact, Mead distinguishes between "inhalation" and "nasal" application. See column 6, lines 45-46. Further, Mead only discusses the addition of complexing agents with respect to "inhalation" embodiments. See column 9, lines 27-36. Accordingly, the skilled artisan would recognize that Mead is acknowledging that the incorporation of a complexing agent, such as EDTA, is not suitable for nasal application. As such, Mead teaches away from adding a complexing agent to a nasal formulation, such as described in Kiechel. Therefore, the skilled artisan would not be motivated to combine Kiechel and Mead in the manner suggested by the Office in an attempt to arrive at the currently claimed

invention. Thus, the necessary motivation for combining Kiechel and Mead is lacking. Consequently, the Office has not proven a *prima facie* case of obviousness.

Since Kiechel, Mead, and any combination of the two, do not teach or suggest all currently claimed elements and the motivation for combining the cited references is lacking, the Office has not proven a *prima facie* case of obviousness. Thus, Applicant submits that these rejections have been overcome. Applicant requests withdrawal of this rejection.

B. Williams in view of Azria/Schwarz and Mead

Claims 1, 2, 5, 12-16, 21, 25-30, 32, 38-40 and 51-69 stand rejected under 35 U.S.C. §103(a) as being obvious over U.S. Patent No. 5,554,610 to Williams et al (hereinafter "Williams") in view of U.S. Patent No. 5,759,565 to Azria et al (hereinafter "Azria") or alternatively in view of U.S. Publication No. 2001/0031738 to Schwarz (hereinafter "Schwarz") and further in view of Mead.

Williams is generally directed to methods of treating disorders associated with pulmonary hypertension by administering a given dose (mg) of a vasodilator, ganglion blocker, sympathetic nerve blocker or calcium channel blocker. Williams teaches that a "unit dose will normally contain 0.01 to 50 mg for example 0.01 to 10 mg, of the Compound, or a pharmaceutically acceptable salt thereof. Unit doses will normally be administered once or more than once a day, for example 2, 3, or 4 times a day, more usually 1 to 3 times a day such that the total daily dose is normally in the range of 0.0001 to 1 mg/kg." See column 2, lines 20-29. Williams provides that such unit doses can be inhaled. The Office acknowledges that Williams does not disclose the recited pH levels, an isotonic formulation, or the addition of complexing agents.

The Office cites Azria and Schwarz for support that it is well known in the art to utilize an isotonic formulation having a pH from 3 to 8 for formulations suitable for inhalation or nasal administration. Azria is directed to pharmaceutical compositions including calcitonin for nasal administration. At column 4, lines 17-24, Azria discloses compositions for nasal administration having a pH from about 3 to 5 and an appropriate isotonicity. Schwarz is directed to formulations for inhibiting endothelial-monocyte activating polypeptide II (EMAP II) by administering a compound that "inhibits EMAP II activity, including compounds that specifically bind to EMAP II (e.g., an antibody), compounds that downregulate EMAP II

expression (e.g., an antisense oligonucleotide), or EMAP II receptor antagonists." Schwarz teaches that the compositions can be made isotonic and a pH of around 6. The Office relies on Mead for teaching a complexing agent.

However, Williams is silent regarding a formulation suitable for localized delivery to the lungs such that a systemic effect is circumvented as recited in independent claims 1, 27, 38 and 51. As recited in independent claim 51 and dependent claims 12 and 57, Williams is also silent regarding an inhalable formulation for local administration to the lungs of a mammal by oral inhalation via nebulization, wherein the formulation is an aqueous suspension comprising a calcium channel blocker. As noted above, the current application was subject to a species election in which Applicant elected to prosecute a formulation comprising a calcium channel blocker. Contrary to the currently claimed invention, Williams only teaches aqueous suspension formulations as being "oral liquid preparations". See column 2, line 60, through column 3, line 7. Further, the oral liquid preparations of Williams are not liquid preparations for oral inhalation as recited in dependent claim 2. The oral liquid preparations of Williams are directed to "syrups, or elixers" that are swallowed, not inhaled. See column 2, line 62. At no point does Williams teach or suggest any inhalable aqueous suspension including a calcium channel blocker, much less being suitable for localized delivery to the lungs of a mammal such that a systemic effect is circumvented. Accordingly, Williams does not teach or suggest all elements of the currently claimed invention.

Similar to Williams, each of Azria, Schwarz and Mead also fail to teach or suggest any of the following: (1) a formulation suitable for localized delivery to the lungs such that a systemic effect is circumvented as recited in independent claims 1, 27, 38 and 51; and (2) an inhalable formulation for local administration to the lungs of a mammal by oral inhalation via nebulization, wherein the formulation is an aqueous suspension comprising a calcium channel blocker. As noted above, the current application was subject to a species election in which Applicant elected to prosecute a formulation comprising a calcium channel blocker. As discussed above, Azria, Schwarz and Mead are silent regarding calcium channel blockers, and thus are also silent regarding an inhalable aqueous suspension comprising a calcium channel blocker. Further, all of the cited references are also silent regarding localized delivery to the

lungs such that a systemic effect is avoided. Since all of the cited references do not teach these elements, any combination of these references also does not teach or suggest these elements.

Additionally, Williams merely teaches dosages (mg) and that these dosages can be provided in a unit dose liquid form. The Office appears to cite Williams for teaching that such unit doses contain from 1 to 5 ml. Therefore, the Office appears to conclude that Williams teaches the claimed concentration or alternatively suggests the claimed concentration ranges. Upon review of Williams, however, Applicant cannot locate any teaching related to a suitable volume for a unit dose. Specifically, Applicant submits that Williams is silent regarding any fill volume suitable for any unit dose preparation, let alone teaching 1 to 5 ml. As such, Williams also does not teach or suggest any of the currently claimed concentration ranges. Further, Applicant submits that not one of the secondary references cited by the Office cures this deficiency nor provides any motivation to modify the dosage teachings of Williams to arrive at the currently claimed invention.

Since Williams, Azria, Schwarz, Mead or any combination thereof all fail to teach or suggest all of the currently claimed elements, Applicant submits that the Office has not established a *prima facie* case of obviousness. Therefore, Applicant submits that this rejection has been overcome and requests withdrawal of this rejection.

V. Provisional Double Patenting Rejection

Claims 1, 2, 5, 12-16, 21, 25-30, 32, 38-40 and 51-69 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting of copending application Serial No. 11/316,458. Since this is a provisional rejection and the Office has not indicated the allowance of any of the pending claims, Applicant will not file a terminal disclaimer at this time. Upon indication of allowable subject matter, Applicant will submit a terminal disclaimer to overcome the rejection.

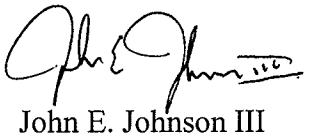
VI. Conclusion

In view of the amendments and remarks made above, Applicant submits that the pending Claims are now in condition for allowance. Applicant respectfully requests that the claims be

allowed to issue. If the Examiner wishes to discuss the application or the comments herein, the Examiner is urged to contact the undersigned by telephone.

It is not believed that extensions of time or fees for net addition of claims are required, beyond those that may otherwise be provided for in documents accompanying this paper. However, in the event that additional extensions of time are necessary to allow consideration of this paper, such extensions are hereby petitioned under 37 CFR § 1.136(a), and any fee required therefore (including fees for net addition of claims) is hereby authorized to be charged to Deposit Account No. 16-0605.

Respectfully submitted,



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